ORAL PHARMACEUTICAL COMPOSITIONS OF FENOFIBRATE HAVING HIGH BIOAVAILABILITY

This application claims priority from Indian Application No. 961/DEL/2002 filed on September 24, 2002.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to oral pharmaceutical compositions of fenofibrate having high bioavailability with improved dissolution and methods for preparing the pharmaceutical compositions.

BACKGROUND OF THE INVENTION

Fenofibrate, 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester, belongs to the family of fibrates or fibric acid derivatives. It is commercially available as oral capsules containing micronized fenofibrate in the strengths of 67 mg, 134 mg and 200 mg. Fenofibrate is indicated as an adjunctive therapy to diet for the treatment for adult patients with very high elevations of serum triglyceride levels who are at risk of pancreatitis and who do not respond adequately to dietary control. It is particularly useful for the treatment of adult endogenous hyperlipidemia, hypercholesterolemia and hypertriglyceridemia.

Fenofibrate is practically insoluble in water and exhibits a low rate of dissolution in aqueous media that results in inadequate bioavailability after oral ingestion. This low rate of dissolution of fenofibrate in aqueous media also is found in gastrointestinal fluids. Several methods of increasing the rate of dissolution of drugs having low solubility in water and other aqueous media have been disclosed in the prior art.

U.S. Patent No. 4,895,726 discloses a fenofibrate composition in which fenofibrate is co-micronized with a surfactant to improve the solubility of the fenofibrate. This patent emphasizes that co-micronizing fenofibrate with a solid surfactant improves fenofibrate bioavailability to a much greater extent than either by adding a surfactant to micronized fenofibrate or intimately mixing fenofibrate and surfactant, micronized separately. In order to further improve the solubility and bioavailability of fenofibrate, U.S. Patent No. 6,074,670 discloses attaining this objective by spraying a suspension of the active pharmaceutical ingredient on a hydro-soluble carrier. U.S. Patent No. 6,277,405 discloses an immediate release fenofibrate composition that includes an inert hydro-soluble carrier covered with at

least one layer containing fenofibrate in a micronized from having a particle size less than 20 μm, a hydrophilic polymer, and an optional surfactant.

SUMMARY OF THE INVENTION

In one general aspect there is provided an immediate release fenofibrate composition comprising an inert hydro-insoluble carrier with at least one layer containing fenofibrate in a micronized form, a hydrophilic polymer and a surfactant; and optionally one or several outer phases or layers.

In another general aspect there is provided an oral pharmaceutical composition of fenofibrate that includes an inert hydro-insoluble carrier having one or more one layers that include fenofibrate in a micronized form, one or more hydrophilic polymers, and one or more surfactants.

Embodiments of the composition may include one or more of the following features. For example, the composition may further include two or more outer phases or layers. The two or more outer phases or layers may include one or more of fenofibrate in a micronized form, one or more hydrophilic polymers, and one or more surfactants.

The composition may have a dissolution of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20 minutes, and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

The micronized fenofibrate may have a size less than or equal to about 20 microns, and more particularly, less than or equal to about 10 microns. The micronized fenofibrate may be present in an amount of from about 20% w/w to about 45% w/w of the composition.

The hydro-insoluble carrier may be one or more of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch. The hydro-insoluble carrier may be present in an amount of from about 20% w/w to about 60% w/w of the composition.

The hydrophilic polymer may be one or more of polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, and gelatin. The hydrophilic polymer may be present in an amount of from about 10% w/w to about 45% w/w of the composition.

The surfactant may be one or more of sodium lauryl sulphate, monoleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids, and propylene glycol laurate. The surfactant may be present in an amount of from about 0.5% w/w to about 3.0% w/w of the composition.

The composition may further include one or more pharmaceutically acceptable excipients that include disintegrants, binders, fillers, glidants, lubricants, colorants, wetting agents, buffers, and coatings. The disintegrant may be one or more of croscarmellose sodium, cross-linked polyvinyl pyrrolidone and sodium starch glycolate. The filler may be one or more of microcrystalline cellulose, lactose, starch, and cross-linked polyvinyl pyrrolidone. The binder may be one or more of hydroxypropyl methylcellulose, hydroxypropyl cellulose, gelatin, and polyvinyl pyrrolidone. The glidant may be one or more of starch, talc, stearates, and colloidal silicon dioxide. The lubricant may be one or more of stearic acid, talc, sodium stearyl fumarate, mineral oil, and magnesium stearate.

The composition may be in the form of one or more of granules, tablets, capsules, dry syrup, suspension, and sachets. The composition may further include one or more of simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, metformin, niacin, folic acid, and losartan. The fenofibrate and the one or more active ingredients may be combined in a single pharmaceutical composition.

In another general aspect, an oral pharmaceutical composition includes from about 20% w/w to about 45% w/w of micronized fenofibrate, from about 10% w/w to about 45% w/w of one or more hydrophilic polymers, from about 0.5% w/w to about 3.0% w/w of one or more surfactants, and from about 20% w/w to about 60% w/w of inert hydro-insoluble carrier.

Embodiments of the composition may include one or more of the features described above or the following features. For example, the micronized fenofibrate may have a size less than or equal to about 20 microns.

The hydro-insoluble carrier may be one or more of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch. The hydrophilic polymer may be one or more of polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose, polyvinyl alcohol and gelatin. The surfactant may be one or more of sodium lauryl sulphate, monoleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene

sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids and propylene glycol laurate. The composition may further include one or more of simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, metformin, niacin, folic acid and losartan.

The composition may have a dissolution of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20 minutes, and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

In another general aspect there is provided a process for preparing a pharmaceutical composition of fenofibrate having an improved dissolution profile. The process includes mixing micronized fenofibrate, one or more hydrophilic polymers and one or more surfactants to obtain a solution or dispersion, and layering the solution or dispersion onto a hydro-insoluble carrier to obtain granulates.

Embodiments of the process may include one or more of the features described above or the following features. For example, the process may further include mixing the granulates with one or more pharmaceutically acceptable excipients selected from the group that includes one or more of fillers, binders, disintegrants, lubricants, glidants, colorants, lubricants, wetting agents, buffers, and flavoring agents to obtain a mixture.

The process may further include processing the granulates to obtain the pharmaceutical composition, wherein the pharmaceutical composition has a dissolution profile of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20 minutes and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

The process may further include processing the mixture to obtain the pharmaceutical composition, wherein the pharmaceutical composition has a dissolution profile of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20 minutes and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

The micronized fenofibrate may have a size less than or equal to about 20 microns, and may be present in an amount of from about 20% w/w to about 45% w/w of the composition.

The hydro-insoluble carrier may be selected from the group that includes one or more of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch, and may be present in an amount of from about 20% w/w to about 60% w/w of the composition.

The hydrophilic polymer may be selected from the group that includes one or more of polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose, polyvinyl alcohol and gelatin, and may be present in an amount of from about 10% w/w to about 45% w/w of the composition.

The surfactant may be selected from the group that includes of one or more of sodium lauryl sulphate, monoleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids, and propylene glycol laurate. The surfactant may be present in an amount of from about 0.5% w/w to about 3.0% w/w of the composition.

The composition may be processed to be in the form of one or more of granules, tablets, capsules, dry syrup, suspensions or sachets.

The process may further include adding one or more of simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, metformin, niacin, folic acid and losartan.

In another general aspect there is provided a method of treating one or more of hyperlipidemia, hypercholesterolemia and hypertriglyceridemia, the method including administering an oral pharmaceutical composition of fenofibrate that includes an inert hydro-insoluble carrier with at least one layer containing fenofibrate in a micronized form, one or more hydrophilic polymers and one or more surfactants.

Embodiments of the treatment method may include one or more of the features described above or the following features. For example, the composition may further include one or more outer phases or layers. The two or more outer phases or layers may include one or more of fenofibrate in a micronized form, a hydrophilic polymer, and a surfactant.

The micronized fenofibrate may have a size less than or equal to about 20 microns, and may be present in an amount of from about 20% w/w to about 45% w/w of the composition.

The hydro-insoluble carrier may be one or more of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch, and may be present in an amount of from about 20% w/w to about 60% w/w of the composition.

The hydrophilic polymer may be one or more of polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, and gelatin, and may be present in an amount of from about 10% w/w to about 45% w/w of the composition.

The surfactant may be one or more of sodium lauryl sulphate, monoleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids, and propylene glycol laurate. The surfactant may be present in an amount of from about 0.5% w/w to about 3.0% w/w of the composition.

The composition may have a dissolution profile of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20 minutes and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

DETAILED DESCRIPTION OF THE INVENTION

Drug efficacy depends in part upon its bioavailability (i.e., absorption into the systemic circulation) to the patient to whom the drug is administered. For drugs that are hydrophobic or poorly soluble in water, increased wettability upon exposure to biological fluids can be an objective for those formulating and manufacturing these agents. Fenofibrate is practically insoluble in water. This insolubility characteristic causes fenofibrate to exhibit a low rate of dissolution in aqueous media, e.g., gastrointestinal fluids, which results in inadequate bioavailability after oral ingestion.

In order to make a pharmaceutical composition of fenofibrate that will provide maximum bioavailability, it is necessary to incorporate into the composition a feature that increases the rate of dissolution of the drug in gastrointestinal fluids. Several ways of increasing the rate of dissolution of drugs having low solubility in water are known in the art. One approach is micronization of the drug whose solubility is insufficient. In this approach, the drug is milled to fine particles, typically having a mean diameter of under about 15 microns. A second approach is to include a surfactant in the composition. For the drug fenofibrate, neither micronization alone nor use of a surfactant alone provides maximum bioavailability. As disclosed above, Laboratories Fournier's patents, U.S. Patent Nos. 6,074,670 and 6,277,405 disclose that by spraying a suspension of the micronized active onto a hydro-soluble carrier, they can increase the bioavailability of fenofibrate.

We have unexpectedly found that contrary to the disclosure of the above prior art, the use of a hydro-soluble carrier is not a prerequisite for improving the bioavailability of fenofibrate and that it is possible to make fenofibrate formulations having improved solubility and bioavailability by spraying a suspension of fenofibrate onto an inert hydro-insoluble carrier. The spraying can be performed such that one or more layers or phases of the fenofibrate are formed on the hydro-insoluble carrier. The composition thus obtained was found to possess a release profile similar to that reported in U.S. Patent Nos. 6,074,670 and 6,277,405.

Micronized fenofibrate as described herein relates to fenofibrate particles having a mean particle size of less than about 20 μm. Particularly, the mean particle size is less than about 10 μm. The compositions generally include from about 20% to about 45% by weight of micronized fenofibrate.

Size reduction, or micronization, may be carried out using any of the conventionally known mills, such as a ball mill, air jet mill, impact mill, etc. Air jet milling is particularly well suited for this application as it is a well proven technique that consistently produces particles of a size less than about 20 microns. Primary advantages of air jet milling are that the predominant particle size reduction occurs through particle to particle collisions, there is limited particle size reduction that results from metal to product contact, and there is no generation of heat that can adversely affect the particles being micronized.

The process of air jet milling involves exposing the material to be micronized to streams of compressed air or gas. Particles in the fluidized bed created by the gas streams are

accelerated towards the center of the mill and collide with the slower moving particles. These collisions break the particles into smaller particles, thereby micronizing the particles. The air jet mills operate by applying opposing air flows and centrifugal forces. By balancing the two forces, desired particle size and fines can be separated.

As used herein, the expression "inert hydro-insoluble carrier" means any pharmaceutically acceptable excipient that is water insoluble and inert. Examples of inert, water insoluble carriers include, but are not limited to, microcrystalline cellulose, dicalcium phosphate, partially pregelatinized starch, and other suitable synthetic and organic polymers. The hydro-insoluble carrier may be present in an amount from about 20% w/w to about 60% w/w of the total weight of the pharmaceutical composition.

The term "hydrophilic polymer" according to this invention should be taken to mean any high molecular weight substance having sufficient affinity towards water. Examples of such polymers include but are not limited to hydroxymethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, gelatin and their mixtures. The hydrophilic polymer may be present in an amount from about 10% w/w to about 45% w/w of the total weight of the pharmaceutical composition.

A surfactant according to this invention may be amphoteric, non-ionic, cationic, or anionic. Examples of such surfactants include but are not limited to sodium lauryl sulphate, monoleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids, propylene glycol laurate, etc. Mixtures of surfactants are also suitable. The surfactant may be present in an amount from about 0.5% w/w to about 3% w/w by weight of the total weight of the pharmaceutical composition.

One suitable process for making the improved bioavailability dosage form includes spraying a suspension of the active ingredient in micronized form and a hydrophilic polymer onto a hydro-insoluble carrier resulting in a pharmaceutical composition of the active ingredient (e.g., fenofibrate) with an improved dissolution profile.

The compositions having improved bioavailability additionally may contain other excipients that are used in the pharmaceutical and chemical fields and are compatible with the active ingredient (e.g., fenofibrate), such as disintegrants, glidants, lubricants, binders, fillers, pigments, wetting agents, buffers, etc.

Examples of disintegrants used in the compositions include but are not limited to those known in the art, such as croscarmellose sodium, cross-linked polyvinyl pyrrolidone, sodium starch glycolate, and mixtures thereof. Example of glidants used in the compositions include but are not limited to those known in the art, such as starch, talc, stearates, colloidal silica, and mixtures thereof. Examples of lubricants used in the compositions include but are not limited to those known in the art, such as stearic acid, talc, magnesium stearate, sodium stearyl fumarate, mineral oil and the like, and mixtures thereof. Examples of binders used in the compositions include but are not limited to those known in the art, such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, gelatin, polyvinyl pyrrolidone and the like, and mixtures thereof. Examples of fillers used in the compositions include but are not limited to those known in the art, such as microcrystalline cellulose, lactose, starch, cross-linked polyvinyl pyrrolidone, etc., and mixtures thereof.

The compositions in accordance with the present inventions may be filled into capsules, formulated as dry syrups, suspensions or mixed with other pharmaceutically acceptable excipients and compressed into tablets. The tablets may further be coated.

Examples of some film forming polymers that can be used for the coating used to coat the compositions include but are not limited to those known in the art, such as cellulose derivatives (hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and their derivatives), acrylic and methacrylic copolymers of different molecular weights, and mixtures thereof.

The compositions generally include, based on the total composition weight, an inert hydro-insoluble carrier representing about 20% to about 60% by weight, micronized fenofibrate representing from about 20% to about 45% by weight, one or more hydrophilic polymers representing from about 10% to about 45% by weight, and one or more surfactants representing about 0.5% to about 3% by weight.

According to one specific embodiment, a process for preparing a pharmaceutical composition of fenofibrate with improved dissolution profile includes the following steps:

a. mixing micronized fenofibrate, one or more hydrophilic polymers, and one or more surfactants to obtain a solution or dispersion;

b. layering the solution or dispersion onto a hydro-insoluble carrier to obtain granulates;

c. mixing the granulates with one or more pharmaceutically acceptable excipients selected from the group that includes fillers, binders, disintegrants, lubricants, glidants, colorants and flavoring agents to obtain a mixture; and

d. processing the granulates or mixture to obtain a pharmaceutical composition having a dissolution profile of at least about 10% in 5 minutes, about 20% in 10 minutes, about 50% in 20 minutes and about 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

The oral pharmaceutical compositions of fenofibrate described herein may be used for the treatment of hyperlipidemia, hypercholesterolemia, and/or hypertriglyceridemia. The pharmaceutical compositions may further include one or more of simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, metformin, niacin, folic acid and losartan. The fenofibrate and the one or more of the active ingredients may be combined in a single pharmaceutical composition.

The following examples further exemplify the inventions and are not intended to limit the scope of the inventions.

EXAMPLE 1

Ingredients	**Percent w/w of composition (%)**
Micronized fenofibrate	23
Pregelatinized starch (core)	39.5
Polyvinyl pyrrolidone	17
Sodium lauryl sulphate	1
Microcrystalline cellulose	14
Cross-linked polyvinyl pyrrolidone	4
Colloidal silicon dioxide	0.5
Sodium stearyl fumarate	1

Process:

Sodium lauryl sulphate was dissolved in water and then the micronized fenofibrate was added to the dissolved sodium lauryl sulphate while stirring continuously. Following this addition, polyvinylpyrrolidone was added while still agitating to form a dispersion. This dispersion was sprayed onto the pregelatinized starch in Glatt process technology using bottom spray. The granulate thus obtained was mixed with cross-linked polyvinyl pyrrolidone, colloidal silicon dioxide, and sodium stearyl fumarate and compressed to form tablets. The tablets thus obtained were film coated.

Tablets of this example 1, herein referred to as tablet I, were compared with Fournier's marketed tablets, herein referred to as tablet II, the formulation having been made in accordance with the invention disclosed in U.S. Patent No. 6,277,405 for dissolution rate. The corresponding release profiles are provided in Table 1.

Table 1: Release profile of tablets prepared according to Example 1 and Fournier's marketed tablets (II) in 1000 ml water/rotating blade method (European Pharmacopoeia)/37°C/75 rpm

Time (Minutes)	Percent Drug Released (%)	
	Tablet I	Tablet II
10	86	84
20	100	98
30	101	100

From the results, it is evident that over 95% drug is released in 20 minutes in both formulations and that tablets I and II show substantially similar dissolution profiles. The formulation containing the hydro-insoluble core also gives a dissolution profile that is similar to that disclosed in U.S. Patent No. 6,277,405, i.e., 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes.

EXAMPLE 2

Ingredients	Percent w/w of composition (%)
Micronized fenofibrate	23
Microcrystalline cellulose (core)	39.5
Polyvinyl pyrrolidone	17
Sodium lauryl sulphate	1
Microcrystalline cellulose (extra granular)	14
Cross-linked polyvinyl pyrrolidone	4
Colloidal silicon dioxide	0.5
Sodium stearyl fumarate	1

Process:

A fenofibrate (micronized) suspension was prepared in a similar way to that of Example 1 and sprayed onto microcrystalline cellulose powder in Glatt process technology using bottom spray to form a granulate. The granulate thus prepared was mixed with a cross-linked polyvinyl pyrrolidone, colloidal silicon dioxide and sodium stearyl fumarate and compressed to form tablets. These tablets were film coated.

The tablets of this example were subjected to dissolution studies using the rotating blade method at 50 rpm according to European Pharmacopoeia in a dissolution medium constituted by 1000 ml water containing 0.025M sodium lauryl sulphate at 37°C. The results are provided in Table 2.

Table 2: Release profile of tablets prepared according to Example 2 in 1000 ml water/rotating blade method (European Pharmacopoeia)/37°C/50 rpm

Time (minutes)	Percent Drug Released (%)
10	53.0
20	75.1
30	85.2
45	91.0

The results indicate that although the speed was reduced from 75 rpm to 50 rpm, more than 90% of the drug is still released in 45 minutes. Thus, it can be concluded that the formulation containing hydro-insoluble core gives a similar dissolution profile to that claimed in U.S. Patent No. 6,277,405 even at a slower rotation speed.

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed inventions and be so described as a negative limitation. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.